



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| (22) International Filing Date: 19 March 1999 (19.03.99)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| (30) Priority Data:<br>60/078,770 19 March 1998 (19.03.98) US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application<br>US 60/078,770 (CON)<br>Filed on 19 March 1998 (19.03.98)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |    | (74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| (54) Title: INHIBITORS OF CASPASES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |    | <b>Published</b><br>Without international search report and to be republished upon receipt of that report.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| (57) Abstract                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p>The present invention relates to novel classes of compounds which are caspase inhibitors, in particular interleukin-1<math>\beta</math> converting enzyme ("ICE") inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting caspase activity and consequently, may be advantageously used as agents against interleukin-1 ("IL-1"), apoptosis-, interferon-<math>\gamma</math> inducing factor- (IGIF), or interferon-<math>\gamma</math> ("IFN-<math>\gamma</math>") mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting caspase activity and decreasing IGIF production and IFN-<math>\gamma</math> production and methods for treating interleukin-1, apoptosis-, and interferon-<math>\gamma</math>- mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.</p> |  |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

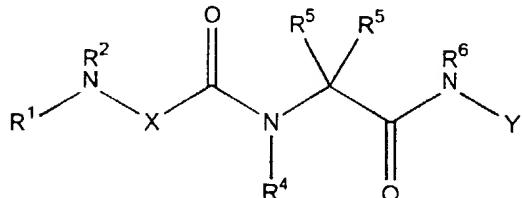
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- 273 -

What is claimed is:

1. A compound represented by formula I:

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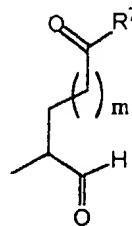
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;

wherein:

Y is:

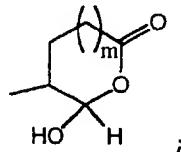
(a)



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provided that when R7 is -OH then Y can also be:

(b)



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X is -C(R<sup>3</sup>)<sub>2</sub>- or -N(R<sup>3</sup>)-;

m is 0 or 1;

30

R<sup>1</sup> is H, -R<sup>8</sup>, -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>,  
 -S(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>,  
 -S(O)N(H)-R<sup>8</sup>, -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>,

- 274 -

$-C(O)CH_2OR^8$ ,  $-C(O)CH_2N(H)R^8$ ,  $-C(O)N(R^8)_2$ ,  $-S(O)_2N(R^8)_2$ ,  
 $-S(O)N(R^8)_2$ ,  $-C(O)C(O)N(R^8)_2$ ,  $-C(O)CH_2N(R^8)_2$ ,  $-CH_2R^8$ ,  
 $-CH_2$ -alkenyl- $R^8$ , or  $-CH_2$ -alkynyl- $R^8$ ;

5  $R^2$  is -H and each  $R^3$  is independently -H, an  
amino acid side chain,  $-R^8$ , alkenyl- $R^9$ , or alkynyl- $R^9$ ,  
or each  $R^3$ , together with the atom to which they are  
bound, form a 3 to 7 membered cyclic or heterocyclic  
cyclic ring system, or  $R^2$  and one  $R^3$  together with the  
10 atoms to which they are bound, form a 3 to 7 membered  
cyclic or heterocyclic ring system, wherein a hydrogen  
atom bound to any -alkyl or -cycloalkyl carbon atom is  
optionally replaced by  $-R^{10}$ , a hydrogen atom bound to  
any -aryl or -heteroaryl carbon atom is optionally  
15 replaced by  $-R^{11}$ , a hydrogen atom bound to any nitrogen  
atom of the ring system is optionally replaced by  $-R^1$ ;

20  $R^4$  is -H and each  $R^5$  is independently -H, an  
amino acid side chain,  $-R^8$ , -alkenyl- $R^9$ , or -alkynyl-  
 $R^9$ , or  $R^4$  and one  $R^5$  together with the atoms to which  
they are bound form a 3 to 7 membered cyclic or  
heterocyclic ring system, wherein a hydrogen atom bound  
to any -alkyl or -cycloalkyl carbon atom is optionally  
replaced by  $R^{10}$ , a hydrogen atom bound to any -aryl or  
25 -heteroaryl carbon atom is optionally replaced by  $R^{11}$ ,  
and a hydrogen atom bound to any nitrogen atom of the  
ring system is optionally replaced with  $R^1$ ;

30  $R^6$  is -H;

$R^7$  is -OH,  $-OR^8$ , or  $-N(H)OH$ ;

each R<sup>8</sup> is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, 5 wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R<sup>10</sup>, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup>, and a hydrogen atom bound to any nitrogen atom is optionally 10 replaced by R<sup>1</sup>;

each R<sup>9</sup> is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is 15 optionally replaced by R<sup>10</sup>, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup>, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>1</sup>;

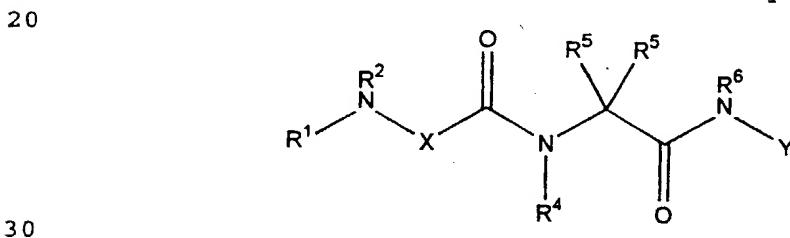
20 each R<sup>10</sup> is independently -OH, -SH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, 25 -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl, -N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl, -N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>, 30 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl, -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>, -alkyl,

- 276 -

-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl,  
 -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or  
 -alkylheterocyclyl, wherein a hydrogen atom bound to  
 any -aryl or -heteroaryl carbon atom is optionally  
 5 replaced by R<sup>11</sup> and a hydrogen atom bound to any  
 nitrogen atom is optionally replaced by R<sup>1</sup>; and

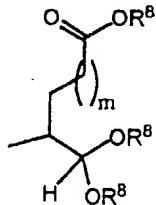
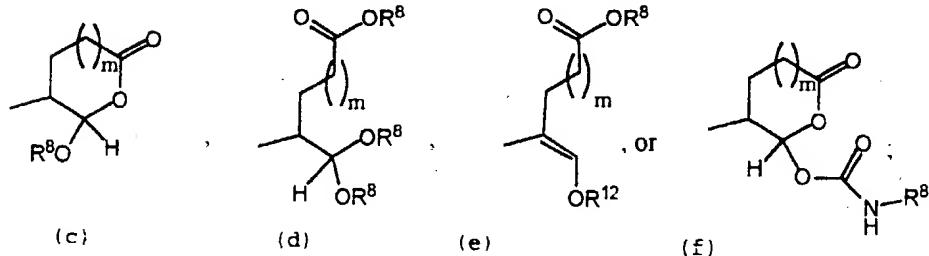
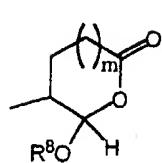
10 each R<sup>11</sup> is independently -OH, -SH, -F, -Cl,  
 -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
 -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-  
 alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl,  
 -N(H)-alkylaryl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl,  
 -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,  
 -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S-aryl, -S-alkylaryl,  
 15 -S(O)<sub>2</sub>alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>,  
 -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>.

2. A compound represented by formula I:

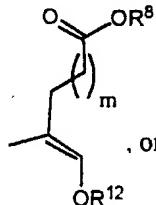


wherein:

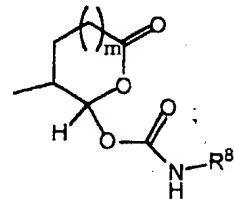
Y is:



(d)



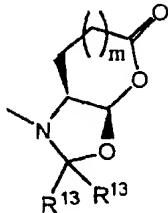
(e)



(f)

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provided that when  $R^6$  is not hydrogen,  $R^6$  and Y, together with the nitrogen to which they are bound, form a ring (g):



5 (g);

X is  $-C(R^3)_2-$  or  $-N(R^3)-$ ;

m is 0 or 1;

10  $R^1$  is H,  $-R^8$ ,  $-C(O)R^8$ ,  $-C(O)C(O)R^8$ ,  $-S(O)_2R^8$ ,  
 $-S(O)R^8$ ,  $-C(O)OR^8$ ,  $-C(O)N(H)R^8$ ,  $-S(O)_2N(H)-R^8$ ,  
 $-S(O)N(H)-R^8$ ,  $-C(O)C(O)N(H)R^8$ ,  $-C(O)CH=CHR^8$ ,  
 $-C(O)CH_2OR^8$ ,  $-C(O)CH_2N(H)R^8$ ,  $-C(O)N(R^8)_2$ ,  $-S(O)_2N(R^8)_2$ ,  
15  $-S(O)N(R^8)_2$ ,  $-C(O)C(O)N(R^8)_2$ ,  $-C(O)CH_2N(R^8)_2$ ,  $-CH_2R^8$ ,  
 $-CH_2$ -alkenyl- $R^8$ , or  $-CH_2$ -alkynyl- $R^8$ ;

20  $R^2$  is H and each  $R^3$  is independently H, an amino acid side chain,  $-R^8$ , alkenyl- $R^9$ , or alkynyl- $R^9$ , or each  $R^3$ , together with the atom to which they are bound, form a 3 to 7 membered cyclic or heterocyclic cyclic ring system, or  $R^2$  and one  $R^3$  together with the atoms to which they are bound, form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is 25 optionally replaced by  $-R^{10}$ , a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally

replaced by -R<sup>11</sup>, a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced by -R<sup>1</sup>;

5 R<sup>4</sup> is -H and each R<sup>5</sup> is independently -H, an amino acid side chain, -R<sup>8</sup>, -alkenyl-R<sup>9</sup>, or -alkynyl-R<sup>9</sup>, or R<sup>4</sup> and one R<sup>5</sup> together with the atoms to which they are bound form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R<sup>10</sup>, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup>, and a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced with R<sup>1</sup>;

15 R<sup>6</sup> is -H;

20 each R<sup>8</sup> is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R<sup>10</sup>, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup>, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>1</sup>;

25

30 each R<sup>9</sup> is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R<sup>10</sup>, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup>, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>1</sup>;

each  $R^{10}$  is independently -OH, -SH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, 5 -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl, -N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl, -N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>, 10 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl, -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>, -alkyl, 15 -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by  $R^{11}$  and a hydrogen atom bound to any nitrogen atom is optionally replaced by  $R^1$ ; and 20

each  $R^{11}$  is independently -OH, -SH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, 25 -N(H)-alkylaryl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>;

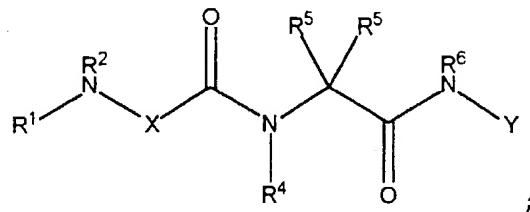
$R^{12}$  is -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkylenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl, -C(O)heterocyclyl, or -C(O)alkylheterocyclyl; and

- 280 -

$R^{13}$  is -H, -alkyl, -aryl, -alkylaryl or -alkylheteroaryl.

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3. A compound represented by formula I:

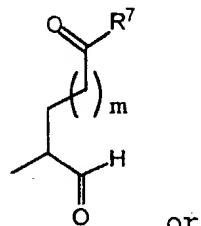


wherein:

$Y$  is:

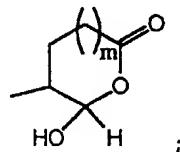
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(a)



or

(b)



15

$m$  is 0 or 1;

$X$  is  $-C(R^3)_2-$

- 281 -

R<sup>1</sup> is H, -R<sup>8</sup>, -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>,  
-S(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>,  
-S(O)N(H)-R<sup>8</sup>, -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>,  
-C(O)CH<sub>2</sub>OR<sup>8</sup>, -C(O)CH<sub>2</sub>N(H)R<sup>8</sup>, -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>,  
5 -S(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>R<sup>8</sup>,  
-CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;

R<sup>2</sup> is -H and each R<sup>3</sup> is independently -H, an  
amino acid side chain, -R<sup>8</sup>, alkenyl-R<sup>9</sup>, or alkynyl-R<sup>9</sup>,  
10 or each R<sup>3</sup> together with the atom to which they are  
bound, form a 3 to 7 membered cyclic or heterocyclic  
ring system, wherein a hydrogen atom bound to any  
-alkyl or -cycloalkyl carbon atom is optionally  
replaced by -R<sup>10</sup>, a hydrogen atom bound to any -aryl or  
15 -heteroaryl carbon atom is optionally replaced by -R<sup>11</sup>,  
a hydrogen atom bound to any nitrogen atom of the ring  
system is optionally replaced by -R<sup>1</sup>;

R<sup>4</sup> is -H and each R<sup>5</sup> is independently -H, an  
20 amino acid side chain, -R<sup>8</sup>, -alkenyl-R<sup>9</sup>, or  
-alkynyl-R<sup>9</sup>, or R<sup>4</sup> and one R<sup>5</sup> together with the atoms  
to which they are bound form a 3 to 7 membered cyclic  
or heterocyclic ring system, wherein a hydrogen atom  
bound to any -alkyl or -cycloalkyl carbon atom is  
25 optionally replaced by R<sup>10</sup>, a hydrogen atom bound to  
any -aryl or -heteroaryl carbon atom is optionally  
replaced by R<sup>11</sup>, and a hydrogen atom bound to any  
nitrogen atom of the ring system is optionally replaced  
with R<sup>1</sup>;

30

R<sup>6</sup> is -H;

$R^7$  is  $-OH$ ,  $-OR^8$ ,  $-N(H)OH$ , or  $-N(H)S(O)_{2R^8}$ ;

each  $R^8$  is independently  $-alkyl$ ,  $-cycloalkyl$ ,  
5  $-aryl$ ,  $-heteraryl$ ,  $-heterocyclyl$ ,  $-alkylcycloalkyl$   
 $-alkylaryl$ ,  $-alkylheteroaryl$ , or  $-alkylheterocyclyl$ ,  
wherein a hydrogen atom bound to any  $-alkyl$  or  
 $-cycloalkyl$  carbon atom is optionally replaced by  $R^{10}$ ,  
a hydrogen atom bound to any  $-aryl$  or  $-heteraryl$   
10 carbon atom is optionally replaced by  $R^{11}$ , and a  
hydrogen atom bound to any nitrogen atom is optionally  
replaced by  $R^1$ ;

each  $R^9$  is independently  $-aryl$ ,  $-heteraryl$ ,  
15  $cycloalkyl$ , or  $-heterocyclyl$ , wherein a hydrogen atom  
bound to any  $-alkyl$  or  $-cycloalkyl$  carbon atom is  
optionally replaced by  $R^{10}$ , a hydrogen atom bound to  
any  $-aryl$  or  $-heteraryl$  carbon atom is optionally  
replaced by  $R^{11}$ , and a hydrogen atom bound to any  
20 nitrogen atom is optionally replaced by  $R^1$ ;

each  $R^{10}$  is independently  $-OH$ ,  $-SH$ ,  $-F$ ,  $-Cl$ ,  
 $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $-NH_2$ ,  $-CO_2H$ ,  $-C(O)NH_2$ ,  $-N(H)C(O)H$ ,  
 $-N(H)C(O)NH_2$ ,  $-perfluoroalkyl$ ,  $-O-alkyl$ ,  $-O-aryl$ ,  
25  $-O-alkylaryl$ ,  $-N(H)alkyl$ ,  $-N(H)aryl$ ,  $-N(H)-alkylaryl$ ,  
 $-N(alkyl)_2$ ,  $-C(O)N(H)alkyl$ ,  $-C(O)N(alkyl)_2$ ,  
 $-N(H)C(O)alkyl$ ,  $-N(H)C(O)Oalkyl$ ,  $-N(H)C(O)Oaryl$ ,  
 $-N(H)C(O)Oalkylaryl$ ,  $-N(H)C(O)Oheteroaryl$ ,  
 $-N(H)C(O)Oalkylheteroaryl$ ,  $-N(H)C(O)Ocycloalkyl$ ,  
30  $-N(H)C(O)N(H)alkyl$ ,  $-N(H)C(O)N(alkyl)_2$ ,  
 $-N(H)C(O)N(H)aryl$ ,  $-N(H)C(O)N(H)alkylaryl$ ,  
 $-N(H)C(O)N(H)heteroaryl$ ,  $-N(H)C(O)N(H)alkylheteroaryl$ ,  
 $-N(H)C(O)N(H)cycloalkyl$ ,  $-S-alkyl$ ,  $-S-aryl$ ,  
 $-S-alkylaryl$ ,  $-S(O)_{2alkyl}$ ,  $-S(O)alkyl$ ,  $-C(O)alkyl$ ,

- 283 -

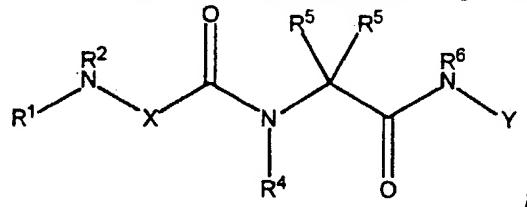
5        -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>, -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R<sup>11</sup> and a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>1</sup>; and

10        each R<sup>11</sup> is independently -OH, -SH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, or -CH<sub>2</sub>N(alkyl)<sub>2</sub>;

15        provided that if one R<sup>3</sup> is -H, then the other R<sup>3</sup> is not -H.

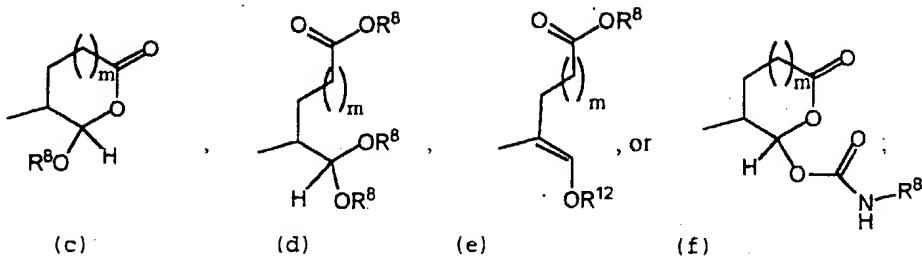
20

## 4. A compound represented by formula I:



wherein:

25        Y is:



$m$  is 0 or 1;

5 x is  $-C(R^3)_2$

10 R<sup>1</sup> is H, -R<sup>8</sup>, -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>,  
 -S(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>,  
 -S(O)N(H)-R<sup>8</sup>, -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>,  
 -C(O)CH<sub>2</sub>OR<sup>8</sup>, -C(O)CH<sub>2</sub>N(H)R<sup>8</sup>, -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>,  
 -S(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>R<sup>8</sup>,  
 -CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;

15        R<sup>2</sup> is -H and each R<sup>3</sup> is independently -H, an  
amino acid side chain, -R<sup>8</sup>, alkenyl-R<sup>9</sup>, or alkynyl-R<sup>9</sup>,  
or each R<sup>3</sup> together with the atom to which they are  
bound, form a 3 to 7 membered cyclic or heterocyclic  
ring system, wherein a hydrogen atom bound to any  
-alkyl or -cycloalkyl carbon atom is optionally  
20        replaced by -R<sup>10</sup>, a hydrogen atom bound to any -aryl or  
-heteroaryl carbon atom is optionally replaced by -R<sup>11</sup>,  
a hydrogen atom bound to any nitrogen atom of the ring  
system is optionally replaced by -R<sup>1</sup>;

25 R<sup>4</sup> is -H and each R<sup>5</sup> is independently -H, an amino acid side chain, -R<sup>8</sup>, -alkenyl-R<sup>9</sup>, or -alkynyl-R<sup>9</sup>, or R<sup>4</sup> and one R<sup>5</sup> together with the atoms